REMARKS

FORMAL MATTERS:

The specification has been amended to reflect the proper use of trademarks. These amendments add no new matter and their entry is respectfully requested.

Claims 1, 7, 8, 13-16, 25, 28-34, 39, 40, 47, 48, 55, 56, and 59-62 are pending after entry of the amendments set forth herein.

Please cancel Claim 12 without prejudice or disclaimer.

Claim 1 is currently amended. Support for these amendments is found at least at Claim 12 and at least in the specification at paragraph [0023] and Figures 1-3.

The Applicants assert that these amendments add no new matter and their entry is respectfully requested.

SPECIFICATION:

The Examiner has objected to the Applicants' lack of trademarks in the specification. The Applicants have corrected the specification to capitalize and include the generic names of trademarked pharmaceuticals.

INFORMATION DISCLOSURE STATEMENT:

The Applicants thank the Examiner for the consideration and for initialing the IDS of November 18, 2004 included with the Office Action mailed February 8, 2008.

REJECTIONS UNDER §103(a)

Claims 1, 7-8, 12, 14-16, 25, and 28-34 are rejected under 35 U.S.C. §103(a) as being unpatentable over Blackburn et al., (U.S. 6,264,825; henceforth "Blackburn") in view of Lizardi et al., (U.S. Patent 5,312,728; henceforth "Lizardi").

In order to establish a *prima-facie* case for obviousness under 35 U.S.C. §103 the Examiner is required to show, *inter alia*, that the prior art references taken together as a whole teach or suggest all claim limitations of the rejected claims.[1] This includes portions of the cited art that would lead away

[1] MPEP § 2141.02(II) Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter "as a whole." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed.

from the claimed invention.[2] Notably, the combination of the references as a whole is still pertinent law under the determination of non-obviousness under *KSR Int'l Co. v. Teleflex Inc.*[3] Moreover, the claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose.[4]

The Examiner has proposed a combination of Blackburn with Lizardi. The Applicants respectfully traverse and assert that the proposed combination taken as a whole does not teach or suggest all claim limitations. Moreover, combination of these disclosures would change the principle of operation of the detector of Blackburn, rendering it inoperable for its intended purpose.

As discussed above, Blackburn teaches a nucleic acid probe bound at one end to a detection electrode substrate and a redox moiety or electron transfer moiety (ETM) bound at the other end. Blackburn does not teach an oligonucleotide probe wherein disruption of internal hybridization results in the second position closer to the electrode as per the present claims. The Examiner relies on Lizardi to overcome the deficiencies in Blackburn.

The Examiner has specifically pointed to Lizardi's Fig. 12 and Fig. 13, which are reproduced below. As illustrated in Fig. 12, the probe is a single stranded RNA sequence containing 5 distinct regions.

Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). See also *Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984) ("treating the advantage as the invention disregards statutory requirement that the invention be viewed 'as a whole'"); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987) (district court improperly distilled claims down to a one word solution to a problem).

[2] MPEP §2141.02(VI) A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)

[3] *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007) as discussed within the context of Examiners applying the *Graham* factors as they relate to the *KSR* holding in the Federal Register: "Ascertaining the differences between the claimed invention and the prior art requires interpreting the claim language, and considering both the invention and the prior art as a whole." Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices, page 57528.

[4] MPEP § 2143.01 ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious." Citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959), in which the court reversed an obviousness rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.).

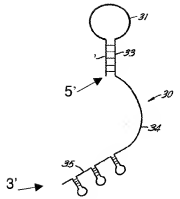


FIG.12

The probe sequence (31) which will hybridize to the target; a first switch (32) at the 5' end of the RNA, a second switch (33), a spacer (34) and a replicatable RNA moiety (35) at the 3' end of the RNA.[5] Each of these five elements is required for operability of the Lizardi probe.

As illustrated in Fig. 13, when the target sequence (8) is bound to the probe sequence (31), it causes a conformational change in the probe, resulting in creation of a ribozyme (36). The ribozyme then acts to cleave the replicatable RNA moiety (35) at the 3' end away from the rest of the probe resulting in two different probe segments as shown below. Thus, in the probes of Lizardi, probe/target hybridization causes the creation of the ribozyme resulting in the **cleavage** of the 3' end of the probe (Lizardi column 14, lines 40-41 and column 13, lines 44-48). The replicatable RNA moiety (35) is then amplified in sufficient amounts for detection by standard RNA detection methods.

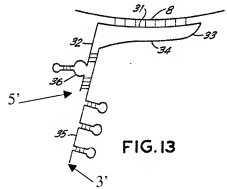
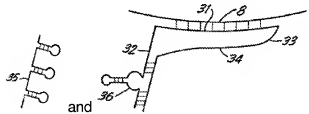


FIG.13

cleavage-> and



The Examiner's proposed combination of Blackburn and Lizardi requires the probes of Lizardi be placed on the detection electrode substrate of Blackburn and conjugated with a detectable ETM. This combination, however, results in destroying the intended purpose of the detector of Blackburn,

[5] Lizardi, col. 14, lines 5-32.

whether the 5' or 3' end of the Lizardi probe is attached to the electrode substrate or the ETM, as either conformation will result in an inoperable probe. If the 3' end (near (35)) of the Lizardi probe is bound to the detection electrode substrate, then the ETM at the 5' end will be cleaved and separated from the rest of the probe when ribozyme acts to cleave the replicatable RNA moiety (35). Because the probe is now cleaved, the ETM will be free and be washed away. The ETM can no longer generate a signal, even though the target sequence has bound to the probe. The replicatable RNA moiety (35) will remain bound to the detection electrode substrate, but this fragment has no means to generate a signal.

The converse is also true. If the probe is anchored to the electrode substrate via its 5' end (near (36)), and the ETM is conjugated to the 3' end, then the majority of the probe will remain conjugated to the detection electrode substrate, but the ETM will still be cleaved, separated from the rest of the probe and washed away. No signal is detected even though a *bona fide* probe/target hybridization has occurred. Thus, modification of the disclosure of Blackburn with the probe of Lizardi not only changes the principle of operation of the Blackburn detector, it renders the Blackburn detector inoperable.

MPEP §2141.02(VI) and supporting case law consideration of the reference as a whole, including those portions which lead away from the claimed invention. The Examiner thus cannot rely on Lizardi for the element of the conformational change in the probe to cure the deficiencies in Blackburn without also considering the disclosure of Lizardi as a whole, which requires the probe be a self-cleaving probe. Thus, the Lizardi reference when taken as a whole does not remedy the deficiencies in Blackburn and does not support a prima facie case of obviousness under which the claims can be rejected.

As such, the combined teaching of Blackburn in view of Lizardi when both references are taken as a whole fail to teach or suggest all of the elements of the currently claimed invention. Therefore, Claims 1, 7-8, 12, 14-16, 25, and 28-34 are not obvious under 35 U.S.C. §103(a) over Blackburn in view of Lizardi and this rejection may be withdrawn.

Claim 13 is rejected under 35 U.S.C. §103(a) as being unpatentable over Blackburn in view of Lizardi and further in view of Rothberg et al., (U.S. Published Application 2002/0012930; henceforth "Rothberg").

As demonstrated above, the combination of Blackburn and Lizardi does not create a prima facie case of obviousness. Modification of the disclosure of Blackburn with the probe of Lizardi not only changes the principle of operation of the Blackburn detector, it renders the Blackburn detector inoperable.

As Rothberg was cited solely for the loop element of Claim 13, Rothberg fails to cure the fundamental deficiency in the combined disclosures of Blackburn and Lizardi.

Accordingly, the combined teaching of Blackburn in view of Lizardi, in further view of Rothberg fails to teach or suggest all elements of the claimed invention. Therefore, Claim 13 is not obvious under 35 U.S.C. §103(a) over Blackburn in view of Lizardi in further view of Rothberg and this rejection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSB-510CIP.

Respectfully submitted,
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Date: May 6, 2008

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